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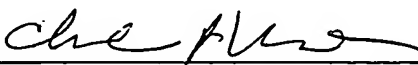
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application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS


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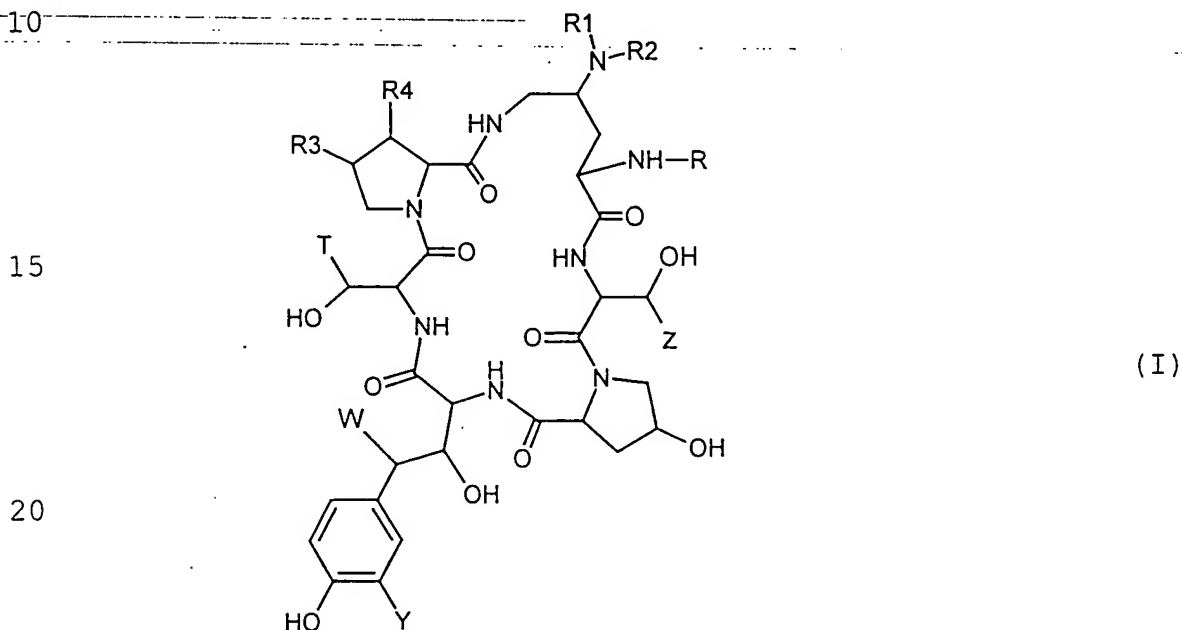
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New derivatives of echinocandine, their preparation process
and their use as antifungals.

---This application is a 371 of PCT/FR00/01569 filed June 8, 2000.---

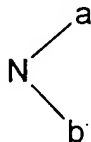
The present invention relates to new derivatives of
5 echinocandine, their preparation process and their use as
antifungals.

A subject of the invention is in all the possible isomer
forms as well as their mixtures, the compounds of formula
(I):



25 in which

either R₁ and R₂ identical to or different from one another,
represent a hydrogen atom, a hydroxyl radical, a linear,
branched or cyclic alkyl radical containing up to 8 carbon
atoms optionally interrupted by an oxygen atom optionally
30 substituted by a halogen atom, an OH radical, an



35 radical, a and b identical to or different from one another,
representing a hydrogen atom or an alkyl radical containing
up to 8 carbon atoms, a and b can optionally form with the
nitrogen atom a heterocycle optionally containing one or more

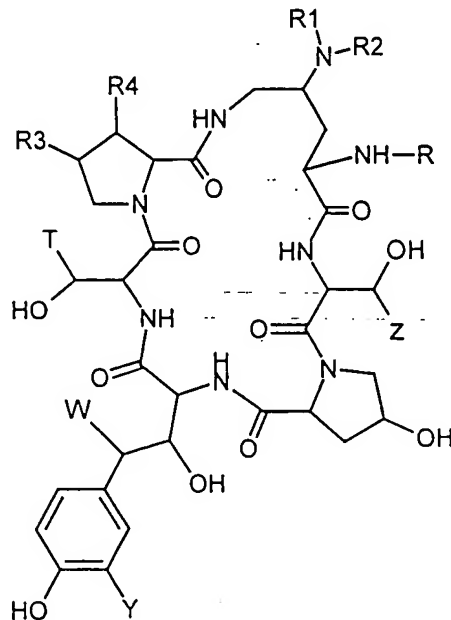
As group selected from the group consisting of

1) ~~in~~ all possible isomeric forms ^{and} as well as their mixtures ~~of~~ the compounds ^{the} of formula (I).

5

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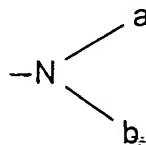
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(I)

20 ~~in which~~ ^{wherein} ~~are individually selected from the group consisting of~~ either R₁ and R₂ ~~identical to or different from one another,~~ represent a hydrogen atom, a hydroxyl radical, ^{alkyl and} ~~a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally interrupted by an oxygen atom optionally~~ substituted by ^{a member selected from the group consisting of} a halogen atom,

~~an OH radical, and~~



~~radical, a and b~~

30

~~are individually~~ ^{of 1} identical to or different from one another, representing a hydrogen atom or ^{or} an alkyl radical containing up to 8 carbon atoms, ^{or} a and b can optionally form with the nitrogen atom a heterocycle optionally containing ^{at least} one ~~or more~~ additional heteroatoms, or R₁ forms with the endocyclic carbon atom

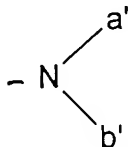
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carrying ~~the~~ $\begin{array}{c} \text{R1} \\ | \\ -\text{N} \\ | \\ \text{R2} \end{array}$ ~~radical~~ a double bond and ~~or~~ R2

5

^{is selected from the group consisting of}
~~represents an-XRa radical, X representing an oxygen, atom or~~
~~an-NH- or-N-alkyl radical containing up to 8 carbon atoms and~~
~~Ra represents a hydrogen atom, a linear, branched or cyclic~~
~~alkyl radical containing up to 8 carbon atoms optionally~~

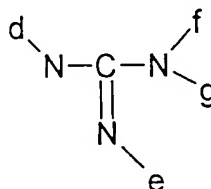
10 substituted by ^{at least one member of the group consisting of} ~~one or more halogen atoms, by one or more-OH,~~
~~-CO₂H, -CO₂alk, radicals, by an~~



15

~~radical, a' and b' representing a hydrogen atom, an alkyl~~
~~radical containing up to 8 carbon atoms, a' and b' can form a~~
~~heterocycle optionally containing one or more additional~~
~~heteroatoms and/or by a heterocycle containing one or more~~

20 heteroatoms or R₂ ^{is} ~~represents a~~

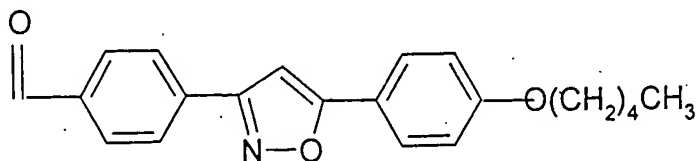


25 ~~radical in which d, e, f and g represent a hydrogen atom or~~
~~an alkyl radical containing up to 8 carbon atoms, f and g can~~
~~moreover represent an acyl radical containing up to 8 carbon~~
~~atoms, e and f can also form a ring optionally containing one~~
~~or more heteroatoms,~~

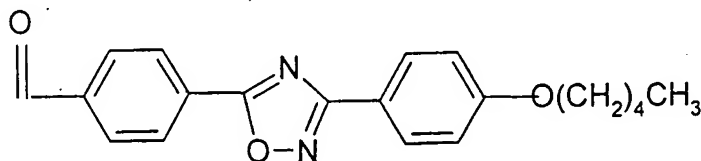
30 ~~R₃ represents a hydrogen atom, a methyl or hydroxyl radical~~

~~R₄ represents a hydrogen atom or a hydroxyl radical~~

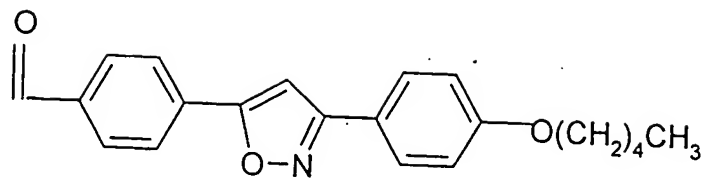
~~R represents a radical chosen from the following radicals:~~



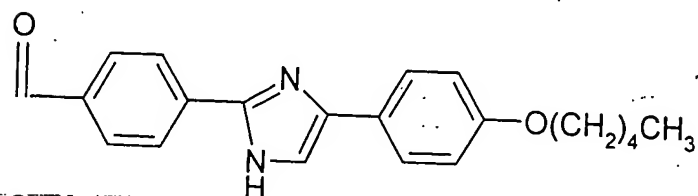
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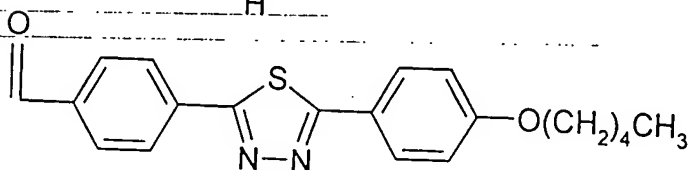
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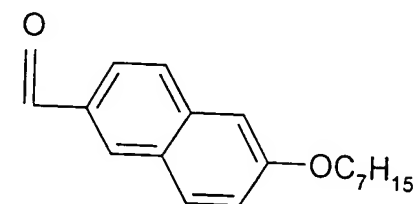
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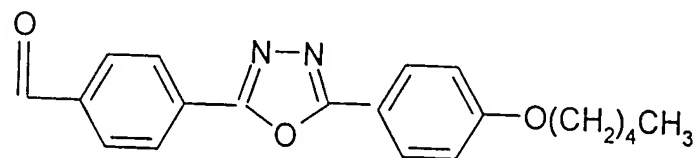
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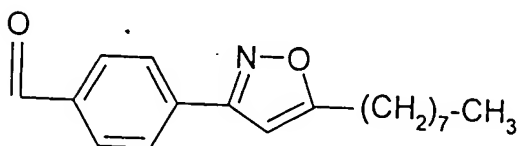
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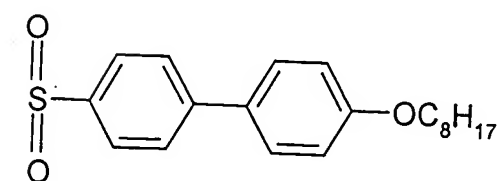
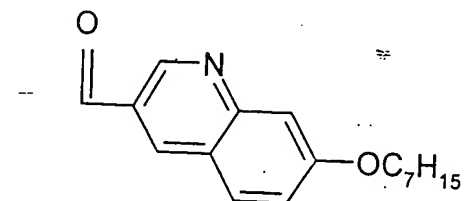
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30



35



and

is selected from the group consisting of

T represents ~~a hydrogen atom, a methyl radical, a~~
~~-CH₂CONH₂, -CH₂CN radical, a~~ ¹⁵~~-(CH₂)₂NH₂ or~~ ¹⁵~~-(CH₂)₂Nalk⁺X⁻ radical, X~~
~~being a halogen atom and alk an alkyl radical containing up~~
~~to 8 carbon atoms,~~

5 Y represents ~~a hydrogen atom, a hydroxyl radical or a halogen~~
~~atom or an OSO₃H radical or one of the salts of this radical,~~
~~W represents a hydrogen atom or an -OH radical,~~

Z represents ¹⁵~~a hydrogen atom or a methyl radical and a non-toxic,~~
~~pharmaceutically acceptable acid~~ ¹⁵~~as well as the addition salts with acids of the products of~~

10 formula (I).

2) ~~The~~ compounds of formula (I) defined in claim 1 in which
T represents ¹⁵~~a hydrogen atom.~~

3) ~~The~~ compounds of formula (I) defined in claim 1 or 2 in
which W represents ¹⁵~~a hydrogen atom.~~

15 4) ~~The~~ compounds of formula (I) defined in any one of
claims 1 to 3, in which Z represents ¹⁵~~a methyl radical.~~

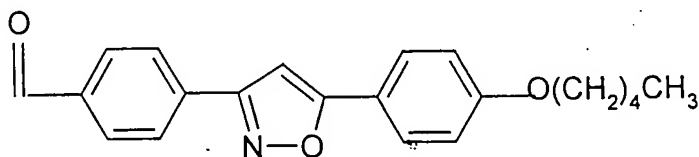
5) ~~The~~ compounds of formula (I) defined in any one of
claims 1 to 4 in which Y represents ¹⁵~~a hydrogen atom.~~

6) ~~The~~ compounds of formula (I) defined in any one of
20 claims 1 to 5 in which R₃ represents ¹⁵~~a methyl radical.~~

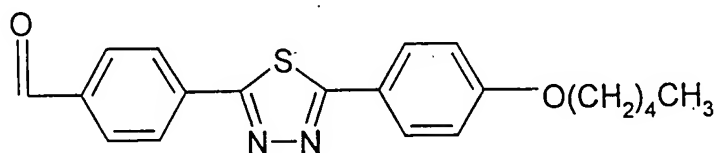
7) ~~The~~ compounds of formula defined in ^{claim 1}~~any one of claims 1~~
~~to 6, in which R₄ represents a hydroxyl radical.~~

8) ~~The~~ compounds of formula (I) defined in any one of
claims 1 to 7 in which R represents ¹⁵~~a~~ *is selected from the group consisting of*

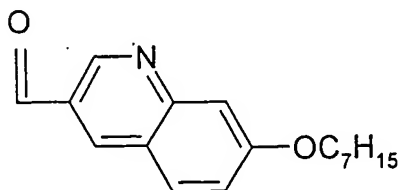
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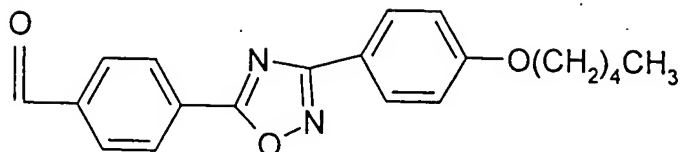
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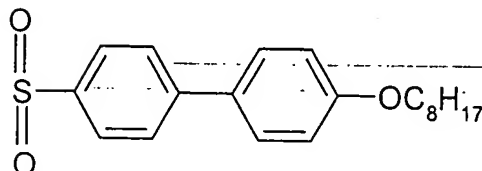
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~~radical~~
~~or a~~

10

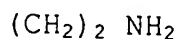
and

15 ~~radical.~~

9) The compounds of formula I defined in any one of claims 1 to 8 in which R_1 ^{is} represents a hydrogen radical.

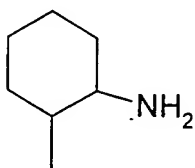
10) The compounds of formula defined in any one of claims 1 to 9 in which R_2 ^{is} represents a

20

~~radical.~~

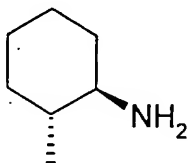
11) The compounds of formula I defined in any one of claims 1 to 9 in which R_2 ^{is} represents a

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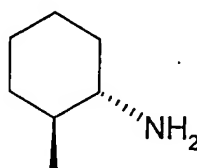
~~radical and in particular the~~

20. A compound of claim 11 wherein R_2 is

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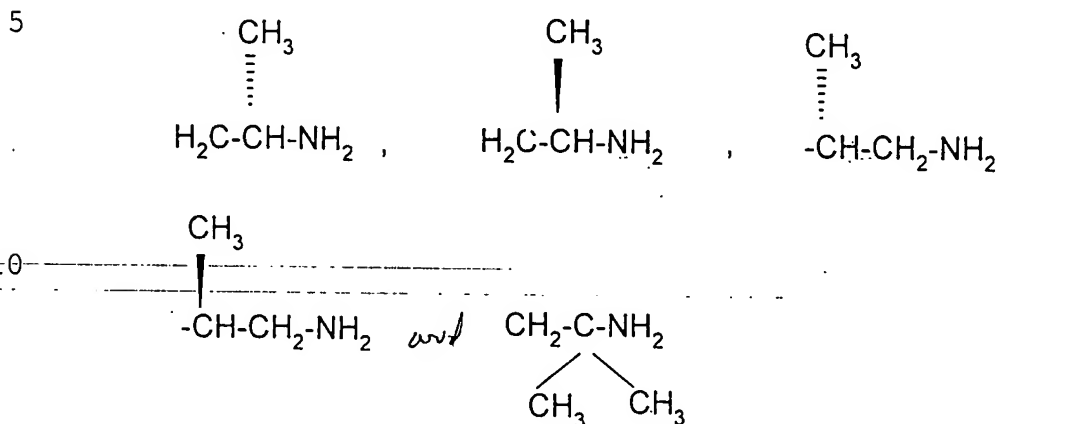


or



radicals.

- 12 ~~12~~ ^A The compounds of formula I defined in any one of claims 1 to 9 in which R₂ ^{is selected from the group consisting of}



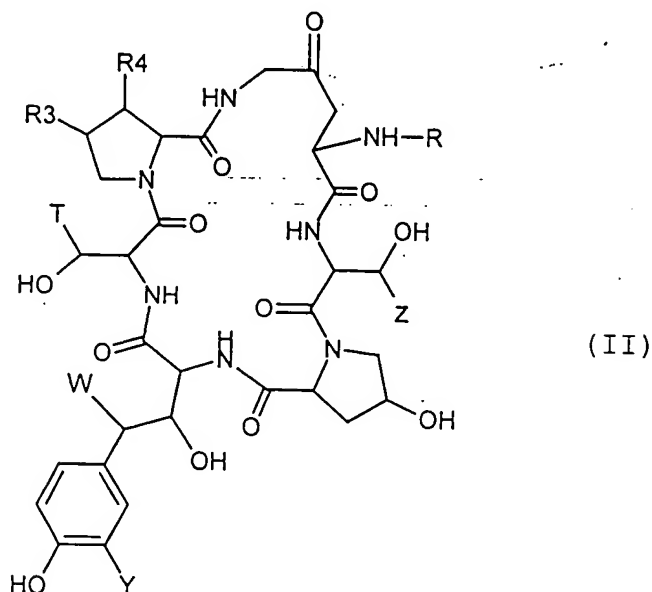
15 radical.

- 13 ~~13~~ ^A The compounds of formula I defined in claim 1 ^{selected from} the names of which follow:

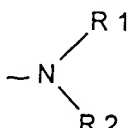
- 1-[4-[(2-aminoethyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans-1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2-aminoethyl) amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate and
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[3-[4-

(pentyloxy enyl]-1,2,4-oxadiazol-5-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate.

14 ~~1A) A process for the preparation of the compounds of formula~~
 5 ~~(I) defined in any one of claims 1 to 13, characterized in~~
~~that a compound of, formula (II)~~



in which R, R₃, R₄, T, Y, W and Z ~~are defined as in claim 1~~ ^{are defined as in claim 1} retain their previous meaning, ~~is subjected to the action of~~ ^{with} an amine or of an amine derivative capable of introducing

25 ~~the~~  radical in which R1 and R2 ~~are defined as in claim 1~~ ^{are defined as in claim 1}

30 ~~retain their previous meaning and if desired to the action of~~ ^{optionally then with}
 a reducing agent,
 and/or ~~of~~ a functionalization agent of the amine,
 and/or ~~of~~ an acid ~~in order to form the salt of the product~~
~~obtained,~~
 35 and/or ~~of~~ a separation agent of the different isomers
 obtained,
 and in this way the compound of formula (I) as defined in
 claim 1 is obtained.

15 ~~15) As chemical products, the compounds of formula (II)~~ ^{the} ~~wherein R, R₃, R₄, T, Y, W and Z are defined as in claim 14.~~ ^(insert)

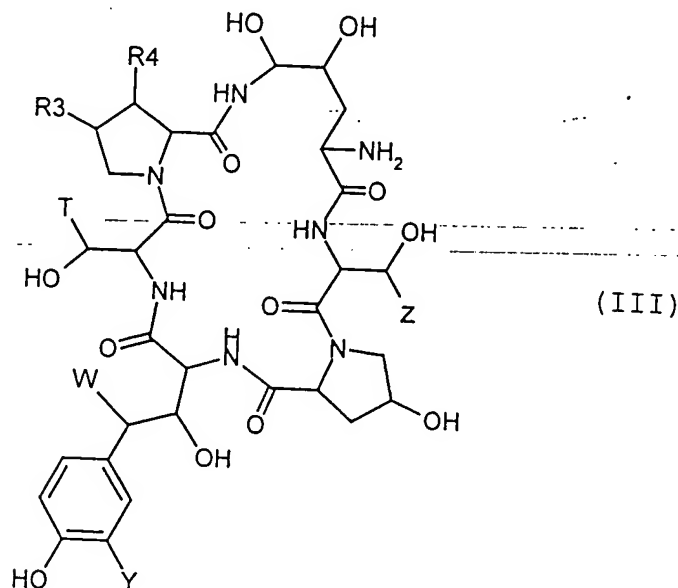
16) A process according to claim 14 ^{wherein} characterized in that a compound, formula (III)

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of the

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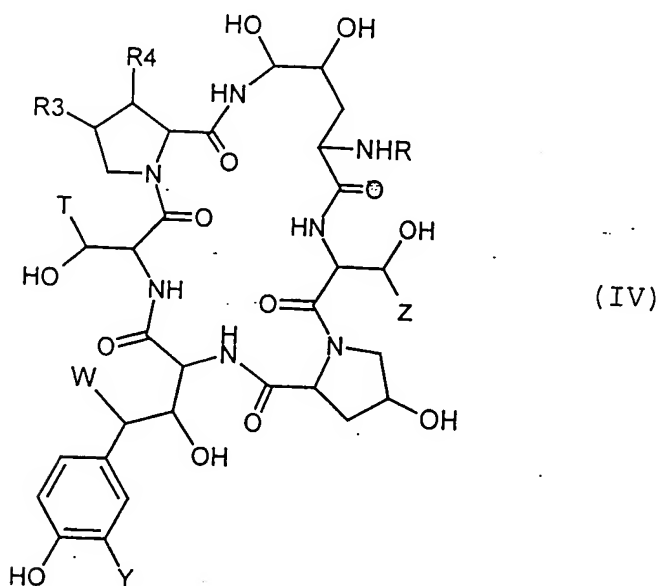


20 ~~R₃, R₄, T, W, Y and Z are defined as in claim 14~~
~~in which the different substituents retain their previous~~
~~meaning is subjected to the action of an agent capable of~~
~~replacing -NH₂ by -NHR, R retaining its previous meaning in~~
~~order to obtain the compound of formula (IV)~~

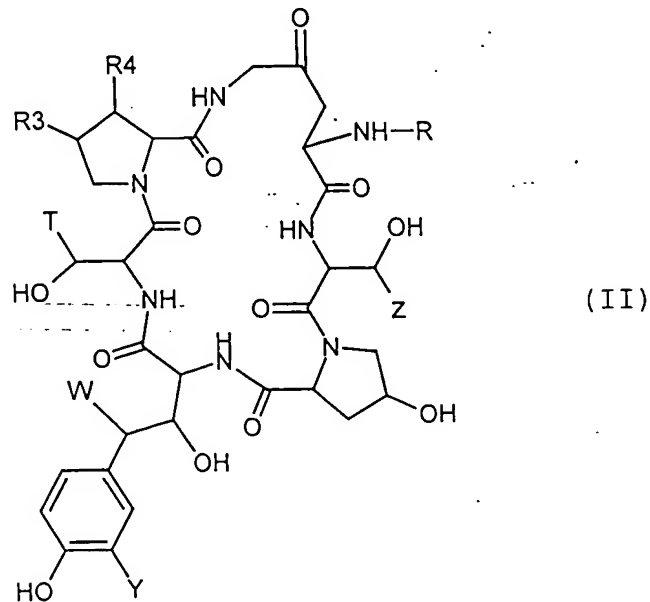
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Reacting said compound with
 which is subjected to the action of trimethylsilyl iodide in
 order to obtain the corresponding compound of formula ~~(I)~~ ^{II}



17) As new chemical products the compounds of formula III and IV defined in claim 16.

20 18) As antifungal compounds, the compounds of formula (I) - defined in any one of claims 1 to 13, as well as their addition salts with acids.

19) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 13
 25 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.